Clustering of cases of IDDM occurring 2-4 years after vaccination is consistent with clustering after infections and progression to IDDM in autoantibody positive individuals.

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Abstract

We previously analyzed data from a hemophilus vaccine trial and identified clusters of extra cases of type 1 diabetes, IDDM caused by the vaccine which occurred between 36 and 48 months after immunization. Published reports indicate clustering of cases of IDDM occurring approximately 2-4 years after mumps infection. Others have reported a 2-4 year delay between the onset of autoantibodies and the development of IDDM. We attempted to determine if similar clustering of cases of IDDM occurred after immunization with vaccines other than hemophilus. We searched Medline and reviewed references from published papers to find databases on the incidence of IDDM and then searched Medline to determine if changes in immunization occurred in these regions during the times the incidence of diabetes was being recorded. Distinct rises in the incidence of IDDM occurred 2-4 years following the introduction of the MMR vaccine and pertussis vaccines. A drop in the incidence of IDDM was detected between 3-4 years following discontinuation of pertussis and BCG vaccines. The data is consistent with the occurrence of clusters following mumps infection and the progression to IDDM in patients with antipancreatic autoantibodies.

Key Words for Medline: Insulin Dependent Diabetes, vaccines, pertussis, BCG, measles, mumps, rubella

Introduction

We previously performed animal studies which conclusively demonstrated a causal link between vaccines and diabetes in NOD mice (1). Data from a large prospective clinical trial supports a causal link between the hemophilus vaccine and type 1 diabeters, IDDM, in humans. In that study we found clusters extra cases of IDDM starting approximately 38 months after immunization and lasting about 6 months (1).

There have been papers published by several different groups of authors which reported clustering of cases of IDDM occurring 2-4 years after infection with mumps virus (2-5). Sultz et al. (2) published epidemiology data that there was a 3 to 4 year delay between mumps epidemics and IDDM epidemics. The authors described a median lag time of 3 years and a mean lag time of 3.8 years between the infection with mumps and the development of IDDM. A group from Finland reported a 2-4 year delay between mumps infection and the development of IDDM (3). The authors also cite two older publications which reportedly contain a similar delay between mumps infection and the development of IDDM (4,5).

Centers in many different parts of the world have prospectively followed the progression to diabetes in individuals with one or more autoantibodies. The delay between the detection of autoimmunity and the development of IDDM is very consistent between centers when looking at similar groups. The studies that are most analogous to the cases of vaccine induced diabetes are in groups of people that have been prospectively followed prior to the development of autoantibodies. In these studies the median onset of diabetes following the onset of autoimmunity is roughly 3 years. There is also about a 2 year delay between the beginning of autoimmunity and the development of any significant number of cases of IDDM.

Researchers have been prospectively following a group of 765 initially non diabetic siblings of diabetic patients in Finland (6), (7). Diabetes manifested after a mean time of 3.2 years from the detection of anti islet cell antibodies in those that were initially negative at the beginning of the study (6). ICA antibodies had the highest sensitivity of any autoantibody with a sensitivity of 100% and presence of a persistent ICA had a actuarial risk of developing IDDM of 47%. The authors found that ICA antibodies had a lower predictive value in controls from the general population than in the siblings of the diabetics (8) which could indicate that those in the general population, as opposed to the siblings, are more likely to have genes that keep the ICA antibodies from destroying pancreatic islet cells. A second study from Finland, prospectively following 4,590 newborns with high and medium genetic risk for developing diabetes (9). The authors found that 95% of all autoantibodies associated with IDDM, including IAAs, GADAs and IA-2s, the sero-conversion occurred in clusters -12 to 8 months around the time of ICA sero-conversion.

A German study prospectively followed children, at risk for developing diabetes because of family history, from birth. Researchers screened blood at birth, 9 months, 2 years, and 5 years. They found that in children who had two autoantibodies by age 2, 50% developed diabetes by age 5, a median onset of approximately 36 months after detection of autoantibodies (10).

Numerous groups have followed the progression to diabetes in high risk patients who have one or more autoantibodies present at the time of enrollment into the study. The median or mean progression time is often near 3-4 years. A group in Finland followed 701 individuals at high risk for IDDM, mean age of 9.9 years. The authors found the median time between the enrollment in the study and the development of IDDM was 3.3 years while the median follow up time for the non progressors was 10.3 years (7). Almost all of those who were ICA positive at the beginning of the study, and went on to develop diabetes, did so within 5 years. A large US study (11) followed 7,834 high risk people (median age 27.4 years) for the development of IDDM, with a median of 4.6 years of follow-up. During the study 135 participants developed IDDM with a median age 10.5 and a median time between the enrollment in the study and the development of IDDM of 2.8 years, similar to the Finnish study above. An group in Italy (12) followed 158 individuals, median age 45, with islet cells antibodies (ICAs) for the development of IDDM. The mean time between the enrollment in the study, ICA positive, and the development of IDDM was 4.8 years. The investigators looked at factors associated with faster progression to development of IDDM in autoantibody positive individuals. They found those with a family history of IDDM, family history of other autoimmune diseases and a younger age may progress to IDDM quicker than others who have the same autoantibodies at the time of enrollment in their study.

We hypothesized that there may be a 2-4 year lag between exposure to a number of different agents causing insult to the islet cells and the development of IDDM. We attempted to determine if clusters of cases of IDDM were detected 2-4 years after administration of vaccines other than the hemophilus vaccine.

Method

Medline was searched to locate publications on the incidence of IDDM in children age 0-14 living in western industrialized nations. Key words used in the Medline search were diabetes, insulin and incidence. References listed in papers found on Medline were used to find additional texts on the subject. We prospectively planned to include only papers on Caucasian populations from Western Europe countries, United States, Canada, Australia, and New Zealand because we felt the standards of living and medical care of the Caucasian populations in these countries were similar and our previous studies had revealed an effect in children living in these countries. We limited our search to papers containing incidence data primarily from 1975 to present and containing at least 100 cases of IDDM in the study population.

After we identified countries with data meeting the criteria mentioned above, a Medline search was performed to determine if changes in immunization practices with the pertussis, diphtheria, tetanus, hepatitis B, polio, hepatitis A, chickenpox, measles, mumps and rubella, BCG, influenza, vaccine occurred during the time frame covered by the diabetes registry. We contacted several sources to determine the details of the discontinuation of the BCG vaccine in Denmark. These included National Board of Health in Denmark, Statens Serum Institut, World Health Organization and others.

Statistical Analyses

Relative risks and other calculations were made using Epi 6 software (WHO). A 2x2 table was with an uncorrected chi square test was used. Taylor series 95% confidence limits were used. Figures on the relative risk were rounded to the nearest tenth. Regarding the BCG analysis, statistics pertaining to the decline in incidence of IDDM in Denmark were described earlier (13). Spearman Rank Order Correlation was performed using the software Statitistica and all 12 pairs of data points from Figure 2. Relative risks were calculated for Finnish populations assuming there were at least 60,000 children born each year. This is a conservative estimate based on data there were approximately 60,000-83,000 children born in Finland each year between 1965-1996 (14).

Results

Rise in the incidence of IDDM In Finland following introduction of more potent pertussis vaccine

The pertussis vaccine has been given in Finland according to a 4 dose regiment starting at 3 months of age with the last booster dose given before 24 months (15). The incidence of diabetes was stable in the 1-4 year old age group in Finland from 1966-1977 at around 15 cases/100,000 per year. In November of 1974 a large clinical trial was started in Finland testing a nonconjugated hemophilus vaccine to a nonconjugated meningococcal vaccine. The study vaccinated approximately 100,000 children between the ages of 3 month to 5 years, or about 25% of all children in Finland of this age (16). Measles immunization was started in Finland in 1975. The vaccine was offered to all children starting at 1 year of age. Immunization rates were about 70% nationally (17). In 1976 the pertussis vaccine was made more antigenic by the addition of a second strain of bacteria (18). Approximately 2-3 years after the addition of the more potent pertussis vaccine an 52% rise in IDDM occurred (19). The incidence rose to 23 cases/100,000 and remained stable from 1978-1986, relative risk of 1.52 ($1.34<RR<1.73$) **(Figure 1A).**

A birth cohort analysis was performed comparing the cumulative incidence of IDDM in those born between 1976-1980, who received the new pertussis vaccine, to children born between 1973-1975, before the new pertussis vaccine was available. Many children in the later group were eligible to receive the new pertussis vaccine as part of a booster dose at age 18-24 months. Children in the 1973-1975 cohort, based on their birth date, may have received the hemophilus/ meningococcal vaccine given in 1974 (16). All children would have been eligible to receive the measles vaccine but at different ages. Data on the cumulative incidence of IDDM in these cohorts was made available from an unrelated study (20). The cumulative incidence in children aged 0 to 4 in the two cohorts to be 82 cases/100,000 and 102.9 cases/100,000 respectively ($P<0.05$), relative risk 1.25.

Decline in the incidence of IDDM during UK pertussis vaccine scare

During the period of 1975 to 1979 immunization with the pertussis vaccine dropped in several countries including the United Kingdom following a published report that the pertussis caused brain damage in children (21). In the UK acceptance rate of the pertussis vaccine fell from 77% in 1974 to 31% in 1978 (22,23). Data from Yorkshire (24) showed a drop in the incidence of IDDM in children age 0-4 which reached a trough in 1982, 3-4 years after the trough in immunization rates with the pertussis vaccine. The incidence of IDDM declined from 9.5 cases of IDDM/100,000 in 1979 to approximately 6.5 in 1982 and rose again to 9.8 in 1985. This is consistent with a relative risk of 1.46 (Spearman Rank Order Correlation $p=.0082$ using all 12 pairs of data points) **(Figure 2)**. The rise in IDDM correlated with the rise in immunization rate. Between 1979 and 1986 the immunization rate went up 75% and the incidence of IDDM rose 85% from 1982-1989 (23).

Measles, mumps, rubella vaccine: Finland

The vaccine regiment in Finland was altered by replacing the measles vaccine with the measles, mumps, rubella (MMR) vaccine at age 14 month and 6 years in 1982 (20). Analysis of incidence data in children age 1-4 shows the incidence of IDDM was stable at a yearly rate of about 23 cases/100,000 from 1977-1985 (14) (**Figure 1A**). The rate rose to 33 cases/100,000 starting in 1986, an relative risk of 1.40 (1.25<RR<1.57) and remained elevated. The delay in the rise of IDDM is consistent with a delay between exposure and the development of IDDM of about 2-4 years.

The incidence of IDDM also rose in the age group 5-9 after the introduction of the MMR vaccine in 1982. The incidence of IDDM varied from 31- 33 cases/100,000 between the years 1976-1981 but stabilized at approximately 39 cases /100,000 from 1982-1993, relative risk of 1.22 (1.11<RR<1.35) (**Figure 1B**). The children born in 1976-1981 had received or been offered the measles vaccine. Comparison of the children exposed to the MMR vaccine, children living in the years 1982-1993 to children who were not exposed to the measles vaccine, children living in the years 1966-1975, indicates the incidence of IDDM had rise to 39 cases/100,000 from 26 cases/100,000 respectively, indicating a relative risk of 1.53 (1.39<RR< 1.67).

Measles, mumps, rubella vaccine: United Kingdom

The measles vaccine was replaced by the MMR in the UK starting in 1988 and given to children around 18 month of age (25). The yearly incidence in children (26) rose from approximately 10 cases per year to 15 cases per year, relative risk of 1.48 (P=0.01), (1.09<RR<2) (**Table 1**). The rise in incidence of IDDM occurred approximately 2-3 years after the introduction of the vaccine.

BCG vaccine

The BCG vaccine was routinely given to school children in Denmark starting at age 7. In 1989 the first county in Denmark officially stopped BCG immunization. BCG was removed from the list of government funded vaccines in 1990 and other counties officially stopped BCG immunization between 1990-1992. However BCG immunization may have declined prior to the official discontinuation. The last available data provided to the WHO indicates 85% immunization rate in 1985 (27). No additional information on immunization rates was available.

Data on the incidence of IDDM, children age 0-14, in 4 counties in Denmark (Fyn, Ribe, Sønderjylland and Vejle) in the years 1989-1993 has been published (28). Additional information on the incidence in the year 1994 was published separately (13) in a paper which also included information on the incidence of IDDM from 1989-1994 in 28 additional countries. The publication on the trends of IDDM in Europe (13) shows Denmark, and only Denmark out of 29 countries, had a statistically significant drop in the incidence of IDDM during the interval 1989-1994. The Incidence of IDDM in Denmark dropped from 18.6 in 1989 to 8.8 in 1994 (**Table 2**). The incidence of IDDM declined 9% per year during this 6 year interval (p= 0.02) assuming a linear decline (13). The trough in the incidence of IDDM occurred about 4 years after the national BCG vaccination programmed was stopped.

Estimates of the relative risk of the BCG varies from 2.1 to 1.6 depending on the method of calculation. If one uses the incidence data in 1994 (8.8 cases/100,000) as the unimmunized incidence and the incidence data in 1989 (18.6 cases/100,000) as the immunized incidence, the

relative risk is 2.17 ($1.28<RR<3.68$), ($p=0.003$). The relative risk, based on an incidence of IDDM declining by 9% per year during the time frame 1989-1994 (13), is 1.61 ($1/.91^5$) .

Discussion

We found that there were clusters of extra cases of IDDM associated with the MMR, pertussis, and BCG vaccine which occurred 2-4 years following immunization. This data is consistent with data from a large clinical trial on the hemophilus vaccine which demonstrated clusters of extra cases of IDDM starting 38 months after immunization and lasting 6 months or more (1). There was insufficient data to determine if clusters of IDDM occur after immunization with the polio, varicella, diphtheria, tetanus, hepatitis A, lyme's, and influenza vaccines. We detected declines in the incidence of IDDM following discontinuation of pertussis and BCG vaccines which are quite notable observation since numerous papers have indicated the incidence of IDDM is rising through out the world (13,29).

Our findings of clusters of IDDM after immunization are consistent with papers from several different groups indicating clusters of cases of IDDM occurring 2-4 years following mumps epidemics (2-5). The clustering of cases of IDDM occurring after vaccination are also consistent with studies on the progression of IDDM in autoantibody positive individuals. In several prospective studies the mean or median time between the detection of autoantibodies and the development of IDDM has been around 3 years (6,10).

The similarities in temporal delay between either infection or immunization and the onset of IDDM compared to the progression of autoantibody positive patients to develop IDDM may be explained by the ability of infections and vaccines to induce the development of autoantibodies. Natural infections with mumps has been linked to the development of islet cell cytoplasmic antibodies (ICA autoantibodies) (30,31). Immunization at birth with BCG vaccine has been associated with decreased risk of diabetes in humans (32) and has recently been associated with a decreased GAD65 and IA-2 autoantibodies (33). The hemophilus vaccine, which has been shown to cause diabetes in humans (1), was evaluated in a case control study using autoantibodies in high risk children (34). While the case control study was small and the results were not statistically, the odds ratio were similar to that seen in the clinical trial with the hemophilus vaccine (1). Islet cell autoantibodies also were found to develop in 3 of 239 10-year old girls following rubella vaccination (35). Furthermore vaccine can cause diabetes in NOD mice, an animal model of IDDM (1). Autoantibody titers especially with antibodies to insulin are strongly associated with the development of IDDM (36).

The 2 year delay between infection or immunization and the development of the cluster is consistent with a progressive autoimmune disease. The data suggests that in most individuals with a healthy pancreas it would take at least two years for autoimmunity to destroy enough islet cells for the person to become diabetic. In older groups containing individuals whose beta cells may have been partially destroyed by prior insults it would be expected that some individuals would develop diabetes soon after immunization or infection. Support for this theory is supplied by data from a US study which followed the development of IDDM in autoantibody positive patients. Over 90% per cent of patients who had an abnormal glucose tolerance at the time of enrollment in the study developed diabetes by 6 years compared to about 55% who had a normal glucose tolerance at the

beginning of the study (37). This may explain our epidemiology data which indicated the Hepatitis B vaccine was associated with rises in the incidence of IDDM starting about one year after immunization (32) in New Zealand.

There are likely many cases of vaccine or infection induced IDDM where the onset of diabetes occurs more than 4 years after immunization. In an analysis of an hemophilus vaccine clinical trial there were an extra 6 cases/100,000 that occurred between ages 7-10 in the group receiving the booster dose of Hemophilus vaccine at age 2 years of age compared to the control (1). These extra cases of IDDM occurred after the cluster. Prospective studies of autoantibody positive patients shows that while most of the patients who progress to IDDM do so before 5 years there are patients who progress to IDDM up to 10 years later (6,7,11,12). These findings are consistent with a delayed, or slowly progressive autoimmune disease, which appears more commonly in studies of older individuals. These findings are also consistent with blood tests showing many older individuals initially diagnosed by Type II diabetes have autoantibodies to their islet cells and actually have an latent autoimmune, Type I diabetes. These individuals often require insulin years after their initial diagnosis (38,39). It is not known why older individuals are likely to have a more slowly progressive disease. Data indicates individuals with the high risk genes develop a rapidly progressive autoimmune disease resulting in IDDM very early in life while others who have moderate risk genes have a slower progressive autoimmune disease and develop IDDM later in life (9). In the later case the autoantibodies may be less cytotoxic the islet cells or the islet cells may have enhanced repair mechanisms to protect the islet cells.

There may be differences between the ability of vaccines to induce IDDM and natural infections (40). Vaccines often contain aluminum and other ingredients which differentiate them from natural infections. Immunization with killed vaccines instantaneously exposes the immune system to a large bolus of immunogens intramuscularly while with natural infections the body is gradually exposed to increasing amounts of immunogen as the organism crosses the mucous membrane and divides. Another difference between natural infections and vaccines is that exposure to natural infections occurred for hundreds of generations prior to the existence of insulin therapy. This would have allowed natural selection to take place and the genes for susceptibility to diabetes, following natural infections, to be removed from the gene pool. This would explain why studies in some populations have found an infectious agent to be diabetogenic and in other populations the agent is not. This could explain discrepancies in studies showing effects and lack of effects by coxsackie viruses.

The current results will help make it easier to detect associations between vaccines and IDDM. In the past there have been discrepancies in results of studies as to whether vaccines were associated with an increased risk of IDDM. Some of the discrepancy can be explained by the study design used (41). Our ability to detect an association between vaccines and IDDM can be attributed to our controlling of confounding effects of more than one vaccine and controlling for the timing of immunization (41). One of the biggest reasons many others have not demonstrated an association between vaccines and IDDM is lack of power. By narrowing the study interval to just the time of the cluster one can increase the power of the study as was shown with the hemophilus vaccine (1). In the current study the relative risk would increase to greater than 2 if the interval of

study was limited to only include the interval between 2-4 years after immunization when the extra cases of IDDM occurred. The relative risk would be smaller if the interval of follow up is extended beyond 4 years. The relative risk would also be decreased if the interval of follow up is shortened so it does not include all the extra cases of IDDM occurring in the cluster spanning the interval 2-4 years after immunization.

The current findings of clusters following immunization are compatible with smaller published studies. Our data indicates the MMR vaccine is associated with an relative risk between 1.43 -1.5, 1.43 (Finland age 1-4), 1.5 (Finland age 5-9), 1.5 (UK age 0-4) over a 4-5 year interval. A large case control study in the United States (42) found the MMR vaccine was associated with an odds ratio of 1.43 or 1.36 depending on compensation of confounding variables. A European multicenter case control study (43) indicated the measles, mumps, and rubella vaccines are associated with odds ratios of 1.02, 1, 1.18 respectively. The same study using a multivariate analysis found that the vaccines were associated with odds ratios of 1.1, 1.03, 1.27 respectively. The combined effect would be an odds ratio of 1.44 (1.1*1.03*1.27) adjusting for confounding variables or 1.2 (1.02*1*1.18) without adjustments. Neither study was powered to reach statistical significance.

A birth cohort study was performed by Hyoty et al. in Finland looking at the affect of the measles mumps rubella vaccine on the incidence of IDDM in Finland (20). Children immunized at age 1 were followed for development of IDDM from birth to age 4. The cumulative incidence of IDDM in children not receiving MMR (born 1973-1975) was 82 cases/100,000 compared to the incidence in children receiving MMR (born 1981-1983) which was 110.6 cases/100,000, relative risk of 1.35. Children immunized at age 6 with the MMR vaccine were followed for the development of IDDM between age 7 and 9. The cumulative incidence of IDDM in children not receiving MMR vaccine (born 1973-1975) was 113.5 cases/100,000 compared to the incidence in children receiving the MMR vaccine which was 121.7 cases/100,000, relative risk 1.07. Our results differ from Hyoty's in part because in Hyoty's study, children were not followed for a full 4 years following immunization, which decreases the relative risk. The children immunized at age 1 were followed for about 3 years, until age 4 while children immunized at age 6 were only followed for less than 3 years following immunization.

Our data indicates a statistical and clinically significant decline in the incidence of IDDM following the discontinuation of the BCG vaccine in Denmark. This decline in incidence is very significant since Denmark is the only country out of the 29 to have a statistically significant decline during this time frame (13). The estimates of the relative risk of 2.17 associated with the BCG vaccine in Denmark is remarkably close to published relative risk of 1.74 based on ecological data (32) comparing the incidence of IDDM in Western European countries which did not give the BCG vaccine to countries that gave the vaccine at school age . The results from Denmark is also remarkably close to an odds ratio of 2.0 based on data from a Canadian case control study (44,45). We analyzed this data to determine the risk of IDDM when the vaccine was given after 1 year of life (44) and found 14 of 249 diabetics had received BCG immunization after 1 year of life versus 12 of 431 controls, odds ratio 2.1 (p=0.06).

Our results indicate pertussis immunization is associated with an increased risk of IDDM. Our studies found the pertussis vaccine is associated with an relative risk of 1.5 (Finland age 1-4) and 1.46 (UK age 0-4). The potential effect of the pertussis vaccine may be larger if one considers the UK study underestimates the effect of the pertussis vaccine because the relative risk assumes the pertussis vaccination rate went from 100% to 0% when in fact it went from 77% to 31%. The Finnish study may have also underestimated the effect of the pertussis vaccine because the study measured the effect of switching from a weaker vaccine to a more potent vaccine. The Finnish study was confounded by the start of measles immunization in Finland in 1975. The birth cohort analysis indicates however that the measles is unlikely to explain the majority of the effect seen because children in the 1973-1975 as well as 1976-1980 birth cohort both received the measles vaccine. Several case control studies (43,46) indicate the measles vaccine alone is not associated with a relative risk of greater than 1.1.

The identification of clusters of cases of IDDM occurring in consistent temporal time periods allowed the link between the hemophilus vaccine and IDDM to be established. The current findings indicate the there is also clusters of cases of IDDM occurring 2- 4 years post immunization with the pertussis, MMR, and BCG vaccine. The data is consistent with the occurrence of clusters following mumps infection and the progression to IDDM in patients with antipancreatic autoantibodies. It is hoped that the discovery of these clusters will help speed the discovery of diabetogenic agents and further the understanding of the pathophysiology of IDDM.

Figure Legends

Figure 1A: In 1976 the Finnish government started immunizing children with a more antigenic pertussis vaccine. The incidence of IDDM rose in children age 1-4 rose about 3 years after the introduction of this new vaccine. The vaccine regiment in Finland was altered to replace the measles vaccine with the measles, mumps, rubella, vaccine and given at age 14 month. The incidence of IDDM which had been stable and again rose in a step like fashion several years after the introduction of the vaccine. Another step like rise in the incidence of IDDM occurred after the introduction of the hemophilus vaccine.

Figure 1B: The incidence of IDDM in Finnish children age 5-9 was stable below an incidence of 27 cases/100,000 in the years 1966-1975. The incidence increased in a step like manner in the years 1976-1981 after the introduction of a more potent pertussis vaccine, an measles vaccine and children in a hemophilus vaccine trial started to reach age 5. The incidence of IDDM rose in a step like fashion again and formed a plateau from 1982 to 1993 after the introduction of the MMR vaccine. Another step like rise in the incidence of IDDM occurred after the introduction of the hemophilus vaccine.

Figure 2: During the period from 1974 to 1978 immunization with the pertussis vaccine dropped in the United Kingdom. Data from Yorkshire showed a drop in the incidence of IDDM in children age 0-4 which reached a trough in 1982, 4 years after the trough in immunization rates with the pertussis vaccine. The incidence of IDDM went from 9.5 cases of IDDM/100,000 in 1979 to approximately 6.5 in 1982 and back to 9.8 in 1985.

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